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Efficacy and Safety of High-dose Vitamin C on Complex Regional Pain Syndrome in Extremity Trauma and Surgery—Systematic Review and Meta-Analysis

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ABSTRACT

Complex regional pain syndrome (CRPS) is a devastating condition often seen after foot and ankle injury and surgery. Prevention of this pathology is attractive not only to patients but also to surgeons, because the treatment of this condition can be difficult. We evaluated the effectiveness of vitamin C in preventing occurrence of CRPS in extremity trauma and surgery by systematically reviewing relevant studies. The databases used for this review included: Ovid EMBASE, Ovid MEDLINE, CINAHL, and the Cochrane Database. We searched for comparative studies that evaluated the efficacy of more than 500 mg of daily vitamin C. After screening for inclusion and exclusion criteria, we identified 4 studies that were relevant to our study question. Only 1 of these 4 studies was on foot and ankle surgery; the rest concerned the upper extremities. All 4 studies were in favor of this intervention with minimal heterogeneity ($Tau^2 = 0.00$). Our quantitative synthesis showed a relative risk of 0.22 (95% confidence interval = 0.12, 0.39) when daily vitamin C of at least 500 mg was initiated immediately after the extremity surgery or injury and continued for 45 to 50 days. A routine, daily administration of vitamin C may be beneficial in foot and ankle surgery or injury to avoid CRPS. Further foot and ankle specific and dose-response studies are warranted.

Complex regional pain syndrome (CRPS) is a devastating condition, common after foot and ankle injuries and surgeries (1). CRPS causes diffuse pain in the extremities that is not isolated to the area of injury or surgery. The condition usually initiates from some form of traumatic stimuli, including injury and surgical intervention (2,3). Patients with this condition often complain of edema, erythema, sudomotor, and motor dysfunctions (2,4,5). Prognosis of this condition is fair when treated early, but becomes poor when it becomes chronic (1,6–8). It has been shown that a high percentage of this condition can involve lawsuits and worker's compensation cases (9). Therefore, prevention of this condition is attractive not only to patients but also to surgeons. Use of high-dose vitamin C has been recommended by the Evidence Based Guidelines for Type 1 CRPS for wrist fractures (10). The recommended intervention consists of a daily, 500-mg dose of vitamin C for a duration of 50 days.

Although the exact mechanism by which vitamin C counteracts CRPS is unknown, the antioxidant property of ascorbate may be responsible for stabilizing free radicals that would normally damage lipid membranes or microcirculation (11–13). Treatment of CRPS with other free radical scavengers has also been studied (14). Vitamin C is a relatively safe supplement that is inexpensive and accessible to many; therefore, if effective, the intervention could be routinely used in foot and ankle trauma and surgeries to great benefit. Our objective in this study was to evaluate the effectiveness of this intervention in preventing occurrence of CRPS in trauma and surgery in the extremities by systematically reviewing and analyzing relevant clinical trials.

Materials and Methods

Inclusion of studies was not limited to those regarding foot and ankle. Studies on surgically and traumatically induced CRPS in the upper extremities were also considered. Only peer-reviewed manuscripts were considered. Intervention of interest was a daily use of vitamin C of more than 500 mg, as recommended by the guidelines (10).

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The outcome measures of interest were development of CRPS after a traumatic event and complications associated with the high-dose vitamin C, if any.

An electronic data search was conducted on August 1, 2012, using a keyword search strategy. Keywords used for this search are listed in Table 1. The databases used for this review included: Ovid EMBASE, Ovid MEDLINE, CINAHL, and the Cochrane Database. No language restriction was set. Google Translate (translate.google.com) was used for translation of foreign languages for screening purposes. All the authors were present in the same room to screen and discuss the articles. Each investigator initially screened the search results independently, and disagreements were discussed among the investigators until agreement was reached.

Inclusion and exclusion criteria are listed in Table 2. After the initial search, the titles were screened for exclusion. The second screening process was performed using the abstract. If an abstract was not available, the actual article was obtained and screened for inclusion and exclusion criteria in the next step. At this point, duplicate studies were eliminated. All the investigators read the remaining articles in their entirety for final selection. Characteristics of each study and potential biases were evaluated and presented using a risk of bias summary chart.

For each study under consideration, we abstracted the number of patients treated with or without vitamin C (or placebo), and for each group, those with CRPS and those without. Using RevMan 5 (Review Manager [RevMan; computer program], Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011), relative risks (RRs) and confidence intervals (CIs) were computed and pooled using the random effects Mantel-Haenszel method. Random effects were used to account for the variability in study populations: elective and emergent surgery, surgical and conservative treatment, and wrist and ankle trauma. When the accumulative RR did not include 1, it was considered statistically significant. Study heterogeneity (Tau^2) was also computed with RevMan 5.

Table 1
Terms used for an electronic search. At least one term from each group had to be in the search for a study to be retrieved

Group 1	Group 2
1. Vitamin C	1. Complex regional pain syndrome
2. Ascorbic acid	2. Reflex sympathetic syndrome
	3. Causalsia
	4. Chronic pain
	5. Algodystrophy
	6. Sudek* atrophy
	7. Sudek* dystrophy

* Truncation.

Results

Our original search identified 281, 106, 26, and 1 articles through EMBASE, MEDLINE, CINAHL, and the Cochrane Database, respectively (Fig. 1). After our initial title screening, the numbers were 68, 18, 11 and 1. Finally, after abstract screening and duplicate elimination, 12 candidate studies were identified.

After reviewing these 12 articles in their entirety, we found that 5 were letters. One of the 12 articles, which came from the Cochrane Database, was a proposed systematic review protocol and not an actual clinical trial. Another was a case series without control or placebo group (15). One was a secondary analysis of the same authors' previous study or cohort (16). This left 4 studies that qualified for our inclusion and exclusion criteria to be used for our final quantitative synthesis (11,17–19). Two of the qualified studies were authored by same investigators (17,18) but on different cohorts. All of the studies had all the data or information needed for our meta-analysis.

One of the comparative studies to evaluate the efficacy of vitamin C on CRPS was published by Zollinger et al in 1999 (18). In their double-blind study, 195 patients were randomly assigned to a placebo group or to a group receiving a 500-mg daily dose of vitamin C. All of the patients had wrist fractures that were treated with immobilization. Patients treated surgically were excluded. A 50-day course of daily oral vitamin C was administered starting on the day of the injury. CRPS was systematically diagnosed by their clinical criteria. There was no reported complication from the high-dose vitamin C. One patient was excluded because she did not take any capsules.

Cazeneuve et al in 2002 published a study comparing 119 patients who underwent surgical management of a distal radial fracture with or without administration of 1 g of vitamin C for 45 days, starting on the day of the fracture (19). During the first 4 years of their study, patients did not receive vitamin C, whereas all the participants who received vitamin C came from last 4 years of the study. The patients were examined up to 90 days after injury to identify CRPS. Diagnostic criteria of CRPS were not described in the article. Two patients had gastrointestinal intolerance and discontinued the high-dose vitamin C during the study period. Neither of them developed CRPS.

Zollinger et al once again evaluated the effect of vitamin C in reducing occurrence of CRPS in their double-blind, randomized clinical trial in 2007, this time in a multicenter study setting (17). They again looked at the efficacy in wrist fractures, but both surgical and immobilized patients were included (331 total patients). They compared daily doses of 200, 500, or 1500 mg of vitamin C versus placebo. The intervention was carried out for 50 days, starting with the day of injury. For our study, those who received less than 500 mg of vitamin C in their study were not analyzed, in order to fulfill our exclusion criteria. Therefore, the group who received the 200-mg dose was not included in our analysis. In their study, CRPS was diagnosed with the clinical criteria described by Veldman et al (4). No patient was lost to follow-up. There was no reported complication from the high-dose vitamin C.

Besse et al investigated the effect of vitamin C in preventing CRPS after foot and ankle surgeries (11). They enrolled 420 patients via a "before-after" quasi-experimental study design. During the first year of the study, the patients did not receive vitamin C. All the participants who received vitamin C came from the second half of the study. The single surgeon who did all the surgeries was also an observer for the study. They used the International Association for the Study of Pain criteria (20) to diagnose CRPS. Their intervention was a daily dose of 1 g of vitamin C starting on the first postoperative day and continuing for 45 days. Their statistician was blinded to treatment group. There was no reported complication from the high-dose vitamin C in the study. One patient was dropped out of the study after discontinuing vitamin C after day 1. The reason for discontinuation was not stated.

Potential biases in these studies are summarized in Figure 3. Both studies from Zollinger et al were double-blind designs and the participants were randomized into either placebo or the vitamin therapy. The other 2 studies had a quasi-experimental design, or were retrospective, without randomization or blinding. A primary outcome measure for all 4 studies was the development of CRPS. There was no detectable reporting bias in any of these 4 studies.

All 4 studies were in favor of prophylactic use of the high-dose vitamin C for prevention of CRPS. Overall, the RR calculated from this quantitative synthesis was 0.22 (95% CI = 0.12, 0.39), which was statistically significant (Fig. 2). Heterogeneity (Tau^2) was 0.00.

Discussion

High-dose vitamin C has been postulated to be beneficial for many conditions (21–32) and is relatively safe in healthy individuals

Table 2
Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Comparative study of daily vitamin C vs. no vitamin C or placebo	1. Having no control group
2. Primary outcome measure is development of CRPS	2. Retrospective studies
3. Intervention of at least 500 mg/day of vitamin C in the "study" group	3. Vitamin C dose of < 500 mg/day
4. Participants having trauma or surgery	4. Injury or surgery in places other than the extremities
	5. Review article written before 2010

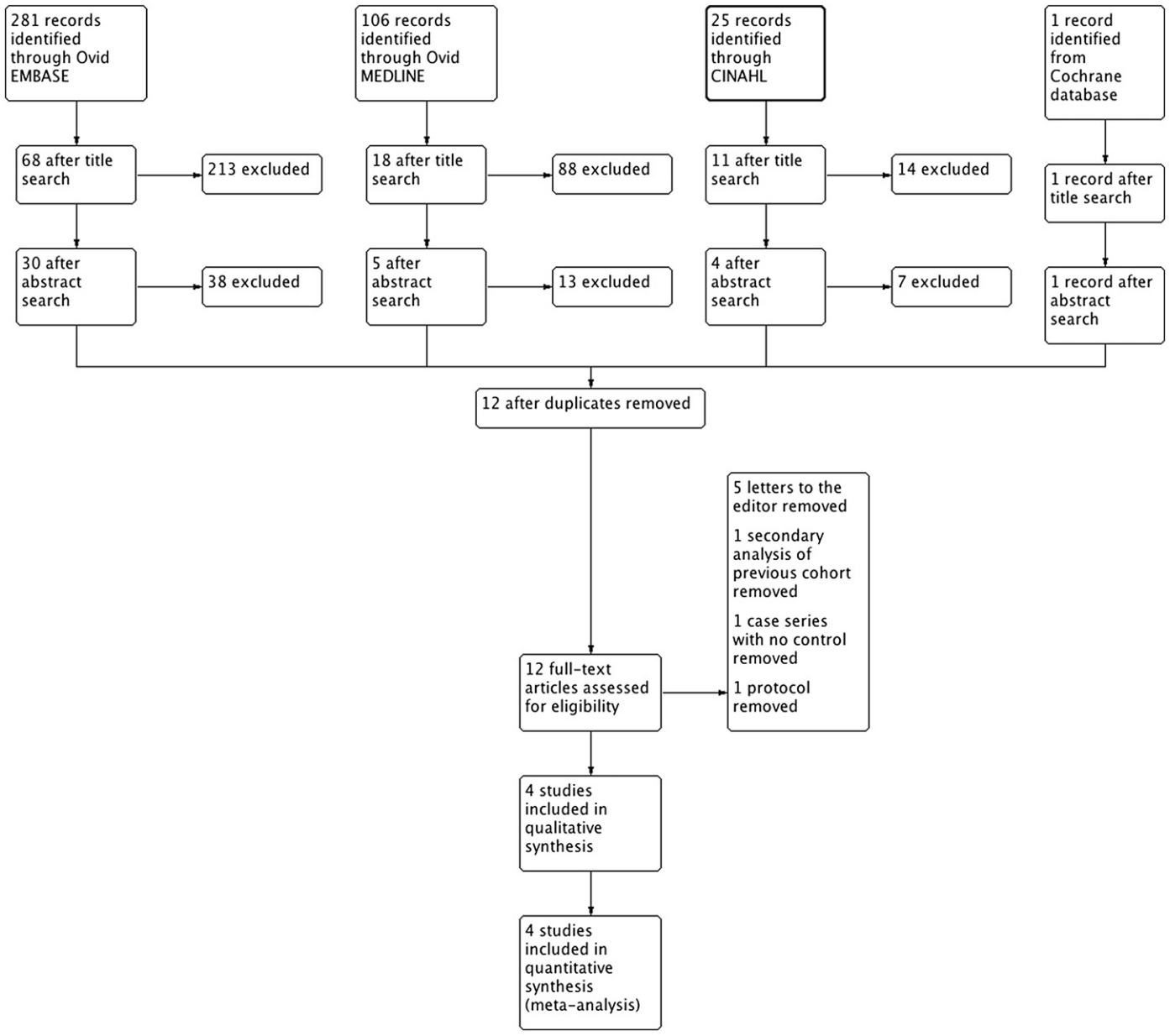

Fig. 1. A study flow diagram.

(22,32–35). However, some adverse effects have been reported. Renal failure has been reported in patients who received a single intravenous high-dose of vitamin C of 2.5 to 45 g (36–38). Also, hemolysis in patients with known glucose-6-phosphate dehydrogenase deficiency has been reported (39,40). The patients in these case reports were receiving intravenous ascorbic acid of 40 to 80 g at a time. All of the patients who had these side effects had severe underlying health issues before the high-dose treatment. No study has been able to control for possible confounders that may be the actual causative factor for these complications. The most common complication from high-dose vitamin C reported from a survey conducted among complementary alternative medicine practitioners was fatigue and

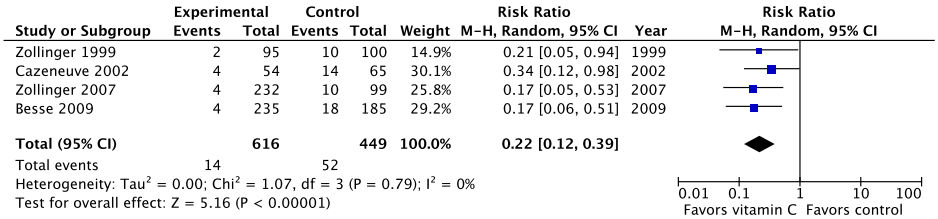

Fig. 2. A forest plot showing RR of developing CRPS when high-dose vitamin C is administered daily for each of 4 studies. A cumulative RR is also presented. For each study the number of cases of CRPS (events) in each arm is shown as compared to all patients within the arm (total).

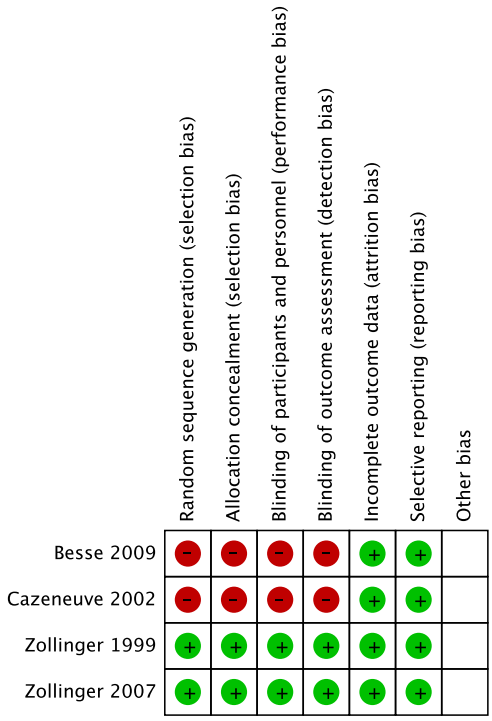

Fig. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. +, Low risk for bias; -, high risk.

lethargy (35). This was reported in 59 of 9328 patients who received an average dose of 28 g every 4 days. It should be noted that the vitamin C dosages in the studies that we reviewed in this article (0.5-1.5 g/day) were significantly lower than in these cases with reported complications.

All 4 included studies independently showed a significant benefit of vitamin C. Our meta-analysis also indicated a statistically significant reduction of CRPS in the group who received the high-dose vitamin C. We feel that this finding is clinically significant: an approximately 5-fold reduction in occurrence of CRPS can be achieved with a daily 500-mg dose of vitamin C, started on the day of trauma. Because vitamin C is inexpensive and relatively safe, this regimen may be used in the practice routinely.

There are a few potential biases in our review process. First, the majority of studies were excluded via the title search. In this process, there may have been some valuable studies that were excluded from our final analysis. However, current guidelines and review articles, as well as the 4 included studies, did not mention any other relevant studies that we potentially missed. Second, we did not include any unpublished data or ongoing projects. We are not aware of any ongoing projects, but we did not methodologically search for these potential data.

We felt that 2 of the 4 studies were at low risk for selection biases because they used a double-blind, randomized study design. It should be noted, however, that the primary authors for these 2 studies were the same. On the other hand, the other 2 studies had no randomization. Vitamin C was not administered in the first part of these studies, but was only received by the participants in the second part of the study. Therefore, investigators and participants were not blinded. Also, their control groups did not receive placebo. Because diagnosis of CRPS was made with clinical criteria and can be highly subjective, these studies are at high risk for potential biases, as the observers were not blinded.

In the clinical setting, CRPS is diagnosed with one or more clinical diagnostic criteria. Many diagnostic tests are available (41–45), but clinical diagnosis is still the gold standard (46–50). Radiographic evaluation of the condition has also been examined in some cross-sectional studies, but it may not have an adequate sensitivity (46,51–53). Therefore, clinical diagnosis as well as research definitions of CRPS must rely greatly on subjective clinical findings. This may be the reason that many lawsuits and worker's compensation cases involve this condition. Similarly, we ought to look at the studies involving CRPS with caution. Again, 2 out of 4 studies we reviewed had a double-blind design, which eliminates the possibility of favoring one group over the other.

Based on our current review, vitamin C, when taken in a daily dose of more than 500 mg for 45 to 50 days post trauma or surgery, may help reduce the occurrence of CRPS after a traumatic event in the extremities. Because it is relatively inexpensive and safe, routine use of this supplement in foot and ankle surgery or injury may be beneficial. A foot and ankle–specific, double-blind, randomized clinical trail would be beneficial to solidify this recommendation.

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